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Three different pharmacological efficacy in a single molecule- phenyramidol

Abstract

Purpose: Phenyramidol was first described pharmacologically in 1959 and is used in the treatment of painful musculoskeletal diseases. In this review, a collective evaluation of *in silico*, *in vitro*, *in vivo*, and clinical studies of Phenyramidol, whose analgesic and myorelaxant efficacy was initially defined, was performed. Our aim was to elucidate the clinical effects, safety, and tolerability profile of Phenyramidol.

Method: Literature was retrieved by a PubMed search, using different combinations of pertinent keywords (e.g., phenyramidol, spasm, pain, musculoskeletal disorders), without any limitations in terms of the publication date and language. Papers that assessed the therapeutic efficacy and tolerability of phenyramidol were selected for inclusion according to their relevance for the topic, as judged by the authors.

Results: In studies, it has been reported that Phenyramidol exhibits an effective and safe analgesic, myorelaxant and anti-inflammatory activity with equivalent analgesic potency to Codeine and Meperidine. It has been shown that with the use of oral or intramuscular Phenyramidol is an effective and safe treatment option that provides up to 94% improvement in painful musculoskeletal disorders and is tolerable in 96.8% of patients. No addictive effects or serious adverse effects on the cardiovascular system have been observed due to oral, parenteral, or concomitant oral and parenteral use of Phenyramidol. It has been reported in studies that oral phenyramidol does not cause any toxicity, does not have an addictive effect, and does not have any significant side effects on the gastrointestinal system even at daily dosages of up to 3200 mg. No serious side effects or mutagenic effects were observed in patients with the use of phenyramidol, and the incidence of side effects was reported to be similar to that of placebo. It has been observed that phenyramidol has strong anti-inflammatory efficacy in silico, in vitro, and in vivo studies, and in addition to having statistically significant higher analgesic efficacy than thiocolchicoside and acetylsalicylic acid, phenyramidol provides anti-inflammatory efficacy equivalent to Ibuprofen and Dexamethasone through balanced cyclooxygenase enzyme inhibition.

Conclusion: Phenyramidol, which contains three pharmacological efficacies that are statistically significant potent analgesic, myorelaxant and anti-inflammatory in studies, is an effective and safe treatment option that provides up to 94% improvement in painful musculoskeletal disorders and is tolerable in 96.8% of patients. Phenyramidol, with its analgesic, myorelaxant and anti-inflammatory effects, is a treatment option that can be used as the first choice in the symptomatic treatment of painful musculoskeletal diseases.

Keywords: phenyramidol, spasm, pain, musculoskeletal disorders

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Introduction

A muscle spasm is a sudden, violent contraction of a muscle or muscle group. When painful, spasms are often called cramps. The anatomical origin of spasms usually includes the muscles, but the mechanism that causes the spasm may be in different areas of the nervous system together with the muscles.[1] Phenyramidol has the chemical structure feature of 2(β-hydroxyphenethylamine)pyridine.[2] Studies on the pharmacological action of phenyramidol have shown that the molecule itself, rather than the metabolites, is responsible for the pharmacological action and the metabolites are relatively inactive.[3] Phenyramidol exerts its muscle relaxant effect by blocking polysynaptic reflexes in the brain and spinal cord.[4]

In addition to its muscle relaxant effect, phenyramidol's analgesic effect was demonstrated in studies conducted in 1959 and 1960. The analgesic effects of phenyramidol were demonstrated for the first time in studies on mice and rabbits. Phenyramidol was found to have an analgesic activity equivalent to codeine when the response to pain induced by temperature stimulation in mice and electric stimulation on the gingiva in rabbits was measured.[5,6]

Other studies have also demonstrated the analgesic effects of phenyramidol.[7,8] In another recent study, it was observed that phenyramidol gave positive results in 7 days of use in patients suffering from low back and musculoskeletal pain.[9] In another study conducted at Ankara University in 2010, the efficacy, safety, and pharmacokinetic properties of the use of phenyramidol in low back pain were also examined.[10] Apart from these studies, recent studies of phenyramidol in silico, in vitro, and in vivo environments have proven that it has anti-inflammatory activity as well as strong analgesic activity.[11]

Overview of clinical evidence

In a clinical study conducted jointly by the New York Medical College and the Metropolitan Medical Center in 1960, it was concluded that the use of phenyramidol is a potent and safe analgesic for use against acute and chronic pain in outpatients and inpatients. In the first group of this study, it was reported that 200 mg Phenyramidol administration in 61 patients suffering from musculoskeletal disorders improved the existing pain status in 34 patients (59%), and undesirable effects were observed in 9 (14.9%) of the patients participating in this

study. In the second group of the same study, in which 44 patients were evaluated, the effectiveness of 200 mg Phenyramidol against placebo was examined and according to the results of this study, it was found that Phenyramidol provided a significant analgesic effect (61.3% effective) in existing pain status in 27 of 44 patients, and undesirable effects were observed in 7 (15.9%) of the patients. In these two studies, the incidence of undesirable effects was found to be similar to each other. As a result of the study, the incidence of side effects of Phenyramidol was found to be similar to placebo.[12]

In the first group of the study, in which the analgesic efficacy of Phenyramidol was investigated in a total of 195 patient groups, 51 patients were administered 100 mg Phenyramidol + 300 mg aspirin combined with a 4x1 posology, and these patients were monitored for 1-22 weeks (mean >2 weeks). In 67% of this patient group, pain improved satiably. However, it has been reported that the incidence of efficacy obtained with the combined use of these agents in arthritic pain is much higher than when these agents have been applied alone, which is also supported by other studies. Adverse reactions observed in patients were mostly observed within the first week. Observed adverse reactions were mild gastrointestinal complaints such as vomiting, epigastric pain, nausea, or itching (with rash/no rash) (4%). Observed adverse reactions resolved as soon as the drug was discontinued.[6]

In the same study, the effectiveness on pain was found to be 54% and the development of adverse reactions was found to be 5%, with the use of Phenyramidol taken four times a day during the 1-12 week treatment period of 43 patients, who were treated as outpatients, constituting the second patient group.[6] The third group of patients evaluated in the study consisted of 61 inpatients, and these patients were treated with 4x1, 200 mg Phenyramidol for 1-7 days of treatment. In this group of patients, it was reported that satisfactory pain relief was observed in 59% of the patients, while the only adverse reaction observed was mild nausea, and this undesirable effect occurred in 6% of patients. Routine blood count and urinalysis of all patients participating in the study were regularly examined throughout this study and for a while after the study ended, and no drug-related abnormality was detected.[6]

In an open uncontrolled prospective study with the participation of 31 patients with acute and chronic spinal painful muscle spasms, a total of 800 mg of phenyramidol (400 mg of phenyramidol at 12-hour intervals) was administered to the patients daily. Pain, spasm, and improvement in functional status were evaluated in patients participating in the study. Statistically significant improvement was observed in all 3 parameters after treatment. While the mean pain before treatment was 5.6±0.8, this value was 3.2±0.9 after treatment; while the mean spasm before treatment was 2.4±0.4, it was 1.5±0.5 after treatment; while the mean functional status before treatment was 2.03±0.7, this value was 1.2±0.4 after treatment. No side effects were observed in 83.9% of the patients participating in the study. The degree of side effects observed was mild and occurred in a short period of time (average 2.4 days). No patient who discontinued the treatment due to side effects were seen. Cabralin spasmolytic and analgesic efficacy were rated as good or very good by 83.9% of patients, and its tolerability was rated as good or very good by 96.8% of patients.[2]

In a study investigating the mutagenic effect of Phenyramidol with the Ames Salmonella/Microsome Test Method, five different concentrations of phenyramidol (0,1, 1, 10, 100, and 1000μg/plate) were tested by inoculating simultaneously 6 petri plates from each control group and concentration series in the presence of solvent, positive and negative controls. As a result of the experiment, the number of colonies that returned with the effect of Phenyramidol were determined. When the data obtained from this study were examined, no dose of Phenyramidol showed a mutagenic effect.[13]

A prospective, randomized and open study was conducted comparing the safety and efficacy of Phenyramidol and Thiocolchicoside in 27 patients with acute spinal muscle spasm. Of the 27 patients who participated in the study, 15 patients received Phenyramidol and 12 patients received Thiocolchicoside injection. The characteristics (age, occupation, etc.) of the patients participating in the study show a homogeneous distribution. No systemic side effects were observed in either patient group. Based on the results of this prospective, randomized, open study, it was concluded that thiocolchicoside 4 mg twice daily for 10 days or Phenyramidol 800 mg once daily constitute an effective and safe treatment in patients with acute painful spinal condition accompanied by muscle spasm. Since Phenyramidol is applied once a day, its use is more advantageous and comfortable than thiocolchicositis. Compared to thiocolchicoside, the mean value of pain intensity was lower and the mean value of effectiveness score was higher in the Phenyramidol group.[2]

In a different clinical study performed in 72 patients with musculoskeletal diseases, the therapeutic efficacy observed with the use of intramuscular phenyramidol was found to be 94%, and the therapeutic benefit obtained by the patients was observed to be close to excellent.[14] In a double-blind study in patients with acute musculoskeletal disorders, phenyramidol in parenteral form was used. In Siegler's study, patients with intramuscular use of phenyramidol showed a statistically significant increase in mobility, a decrease in pain and spasm compared to placebo. It has been reported that phenyramidol is an effective option in the treatment of musculoskeletal diseases with spasms and pain.[15] Renta's study compared the intravenous and intramuscular use of phenyramidol. It has been shown that Phenyramidol statistically reduces pain intensity and muscle spasm intensity to a significant degree.[3]

In a study conducted in 166 patients with orthopedic disorders in 1967, the analgesic efficacy was reported as "good" by 9 patients and "satisfactory" by 6 patients following administration of Phenyramidol to 16 patients with the acute cervical syndrome. In 35 patients with a diagnosis of chronic cervical syndrome-cervical osteochondrosis, it was shown that the pain status of 22 patients improved at a "good" level as a result of using Phenyramidol. Phenyramidol given to 24 patients diagnosed with acute lumbago with sciatica improved the pain in 12 patients to a "good" level. Phenyramidol was used in 24 patients diagnosed with myalgia, and the pain was improved in 15 patients at a "good" level. As a result, a good and satisfactory effect was obtained in 85% of 166 patients with Phenyramidol treatment. During the study, no serious side effects were observed in the patients participating in the study.[16]

In a clinical study involving 48 patients, where Epicondylitis was observed in 13 patients, forearm and hand tenosynovitis in 3, bursitis in 5, myositis in 16, muscle cramps in 1, confusion in 6, sprain in 2, and thumb and finger fractures in 2, phenyramidol or phenyramidol+aluminum salicylate combinations were administered every four to six hours to these patients, and treatment was continued for 1 week when necessary. It was observed that 34 of 48 patients responded well enough to be called "excellent" when treated with phenyramidol alone, and 5 patients responded "good", 2 patients "poor", and 7 patients "insufficient". In 9 out of 15 patients with epicondylitis, treatment with phenyramidol alone provided an excellent response. In 3 patients with a diagnosis of tenosynovitis, a "good" response to the combination of aluminum salicylate +

phenyramidol was observed. Pain relief was observed in 14 of 16 patients diagnosed with myositis with the use of aluminum salicylate + phenyramidol combination. Phenyramidol treatment has been observed to significantly increase the range of motion of the joint in patients with post-fracture joint stiffness. In patients with severe pain, 200 mg of phenyramidol + 600 mg of aluminum salicylate was administered every four hours, and the highest efficacy was observed with this posology.[7]

In a double-blind, randomized clinical trial investigating the degree of dependence of phenyramidol and carisoprodol, seventeen tests were performed in the 100-750 mg dose range using intolerant subjects; maximum dose (750 mg) of phenyramidol was administered to 6 patients, and no undesirable side effects were reported, except for "drowsiness", which was reported in only one of these patients. In the same study, when the degree of addiction of orally administered carisoprodol and phenyramidol were examined, it was observed that neither carisoprodol nor phenyramidol had addictive properties.[17]

In a clinical study examining whether phenyramidol potentiates the effect of anticoagulants, in addition to 2 patients whose history and findings are known in detail, 9 patients who received long-term anticoagulant therapy, 6 patients who did not receive anticoagulant therapy, and 4 hospital staff participated. Phenyramidol was given orally to the participants at a daily dose of 800 mg, and this dose was increased up to 1600 mg when necessary. A remarkable decrease in the percentage of prothrombin time was determined after the administration of phenyramidol in patients using warfarin sodium, bishydroxycoumarin, or phenindione. This effect was seen in some participants 3 days after starting phenyramidol, and this decrease was sustained for seven days in 9 of 10 patients. 10 patients who did not take anticoagulants were given 1600 mg of phenyramidol daily for an average of 8 days. There was no significant change in prothrombin time in this group.[18]

In a clinical study in which a double-blind comparison of intramuscular phenyramidol and placebo in acute musculoskeletal pain syndromes was made, 70 patients who came to the orthopedics clinic were included in the study. Patients suffered from myospastic conditions such as sprains, fractures, torticollis dislocations, bursitis, hemarthrosis, and supraspinatus syndrome. Each patient's pulse, blood pressure, range of motion, degree of pain, and degree of muscle spasm were evaluated and recorded prior to injection. In the study, 35 patients received a placebo and 35 patients received intramuscular phenyramidol, and the use of phenyramidol showed statistically higher efficacy in pain relief compared to placebo ($p<0.025$). Similarly, the efficacy of phenyramidol on muscle spasms was statistically significant compared to placebo ($p<0.001$). Out of 35 patients, who received a placebo, dizziness was observed in 1 patient, and a slight decrease in blood pressure was observed in 1 patient. Of the 35 patients receiving phenyramidol, 3 experienced a decrease in blood pressure, which was mild in 2 and more severe in 1 patient. This reduction in blood pressure did not require drug discontinuation in any patient using phenyramidol.[15]

In a study on mice to investigate the presence of a cholesterol-lowering effect, Phenyramidol was injected intraperitoneally once a day for 14 days. At the end of the study, intraperitoneal administration of Phenyramidol for 2 weeks reduced the serum cholesterol concentration of mice by 36%. The cholesterol reduction rate of oral phenyramidol administration was 23%. In the follow-up study of the same study performed in 5 male and female patients, it was shown that the use of phenyramidol for 2 weeks resulted in an average of 24% reduction in serum cholesterol. In addition, no reported adverse effects were observed in the study participants.[19]

In a clinical study conducted with 69 patients with painful musculoskeletal disorders such as postoperative lumbar disc rupture, cervical or lumbosacral strain, phenyramidol was initially administered to these patients at 200-400 mg orally 4 times a day, then added to the patients' treatment simultaneously at appropriate intervals, and dosing was gradually increased from 25 mg to 500 mg until the ideal dose was determined for intravenous administration. Concomitant administration of oral and intravenous Phenyramidol has been shown to improve the majority of patients with severe muscle spasms. Less than 3% of patients in the study experienced side effects (dizziness, feeling of warmth, numbness of the tongue, metallic taste in the mouth). However, it was observed that these side effects were not at a level that caused the patients to discontinue the treatment and that 91% of the 69 patients studied provided a satisfactory clinical response from the phenyramidol treatment.[20]

In the first phase of a double-blind randomized 2-stage study examining the effect of parenteral administration of phenyramidol on muscle spasm, the efficacy of Phenyramidol on muscle spasm was examined, while this effect was compared with Methocarbamol in the second study. A total of 146 patients were included in the study, and it was reported that the common problem in all patients was "acute muscle spasm". While 52 patients were included in the first stage, 94 patients were included in the second stage. In the first stage, patients were given a dose of 3.5 mg/kg i.m. phenyramidol injection. In the first stage, after the administration, 35 patients stated that their existing pain was healed at an "excellent-good" degree (67.3%), while 34 patients reported that their existing muscle spasms improved (65.4%). In the second stage, 0.2 g/ml phenyramidol i.m. injection was administered to 47 patients, while the remaining 47 patients were administered with 0.1 g/ml Methocarbamol i.m. injection. In this group, the patients were randomly selected and the existing pain status and range of motion of the patients in the second group were evaluated by grading (between -3 and +6). The result of ratings for the efficacy of Phenyramidol was 5.7 on average, versus 4.7 for Methocarbamol. As a result of the study, it was shown that Phenyramidol is a significantly more effective treatment option in relieving spasms compared to Methocarbamol ($p:0.03$). No adverse events were reported after the administration in any of the patients participating in the study.[21]

In a clinical randomized trial, where efficacy, safety and pharmacokinetic parameters of oral and i.m. phenyramidol administration was evaluated, 72 patients were included in the study, randomized (5:3) for 800 mg oral and i.m. phenyramidol treatment. It has been shown that the low back pain of the participating patients (45F/27M) decreased significantly without any difference between the two groups. It was reported that 7 of the 38 patients included in the study showed increases in liver enzymes that returned to normal levels after a 1-week follow-up. As a result of the study, it was emphasized that the liver enzymes of patients using long-term phenyramidol should be monitored and that it should not be administered together with analgesics with liver toxicity such as paracetamol. As a result of the studies, it was determined that both forms had similar efficacy and safety, and it was reported that none of the side effects observed during the study period were at a serious level.[10]

In a study examining the efficacy of oral Phenyramidol in 225 patients with dysmenorrhea, the patients were divided into 3 groups: the first group consisted of 75 patients with severe dysmenorrhea between the ages of 16-34; the second group involved 50 female patients between the ages of 16-42 with premenstrual tension headache; in the third group, the efficacy of using phenyramidol in combination compared to the Codeine combination in relieving postpartum pain was evaluated in 100 female patients. In the

first group, the participants were initially given 200-400 mg of phenyramidol. The current clinical status of 74.6% of patients in this group improved to an "excellent" degree. In the second group, 200-400 mg of phenyramidol was given to the patients initially, and the patients were asked to repeat the dose within 1 hour of taking the initial dose if deemed necessary. The current clinical condition of 70% of the patients in this group also improved to an "excellent" degree. In the third group, some of the patients were given a combination of 200 mg phenyramidol+ 325 mg acetylsalicylic acid, and 32.5 codeine sulfate + 650 mg acetylsalicylic acid combination. Among the patients in this group, 80% of the patients who received the combination of phenyramidol + aspirin had an "excellent" improvement in pain, while this rate was 79% for the patients who received the combination of codeine sulfate + acetylsalicylic acid. As a result of the study, the combination of phenyramidol and acetylsalicylic acid was found to be as effective in relieving pain as the combination of codeine sulfate + 650 mg acetylsalicylic acid. Combination Sensitivity developed in 1 of the patients who received the phenyramidol combination, while the combination sensitivity developed in 2 patients who received the codeine sulfate combination. In the study, it was shown that Phenyramidol provides relief in complaints such as dysmenorrhea and premenstrual tension, and headache. In addition, it was concluded that the combination of Phenyramidol + Acetylsalicylic acid could "successfully" relieve postpartum pain. This has led to the conclusion that phenyramidol is an agent that can be preferred with its rapid analgesic effectiveness starting at 15 minutes, even when narcotic analgesics are required.[22,31]

In the clinical study performed in 75 patients (age range 16-34 years) with severe dysmenorrhea who were prescribed phenyramidol, oral Phenyramidol therapy was administered from 200 mg to 400 mg, with a maximum daily intake of 3200 mg, immediately after the onset of cramps. As a result of the study, Phenyramidol demonstrated efficacy in 65 patients with an "excellent" and "good" grade of 87% and a "poor" grade (13%) in 10 patients. In the study, it is reported that the use of Phenyramidol in patients with dysmenorrhea can provide equivalent efficacy without the side effects associated with the use of codeine and antihistamine. In addition, Phenyramidol's other advantages are that it does not have an addictive effect and does not have any significant side effects on the gastrointestinal tract compared to codeine and acetylsalicylic acid. It has also been shown in the same study that phenyramidol has a safe use at high doses.[8]

In a study of 50 primary dysmenorrhea patients with severe premenstrual headache, aged between 16-42 years of age, Phenyramidol was administered from 200 mg to 400 mg orally, immediately after the onset of cramps, and the daily intake was limited to a maximum of 3200 mg. As a result of the study, it was observed that the use of oral phenyramidol provided "complete and satisfactory relief" in 80% of primary dysmenorrhea patients.[8] In a clinical study comparing the efficacy of phenyramidol as an analgesic in clinical use with standard analgesics, patients with moderate-to-severe pain with different characteristics of musculoskeletal diseases were examined. Patients were randomly divided into three groups in the study. 155 patients with acute pain in the first group and 176 patients in the second group were evaluated, in the first group, 100 mg Phenyramidol was given to 43 of 155 patients, 200 mg Phenyramidol was given to 61 patients, and a combination of 100 mg Pheniramidol + 300 mg Acetylsalicylic acid was administered to 51 patients. In the second group, in which the efficacy of phenyramidol was compared with standard drugs, 49 patients were given a placebo, 87 patients acetylsalicylic acid (600 mg), and 40 patients sodium salicylate (600 mg). All drugs applied in the studies were administered 4 times a day and treatment was continued for an average of 2 weeks for each patient. As a result of the study, the pain status of the participants was evaluated by physicians and patients, and a satisfactory analgesic effect was observed in 53.6% of patients receiving 100 mg Phenyramidol, 59% of patients receiving 200 mg Phenyramidol, and 66.6% of patients receiving 100 mg Phenyramidol+ 300 mg Aspirin. For other analgesics, this efficacy rate was 51.7% for Aspirin (600 mg) and 50% for sodium salicylate. As a result of the study, it was determined that all doses of Phenyramidol exhibited more successful efficacy compared to standard drugs. It has been determined that the analgesic effect starts as soon as the drug is taken and continues for 3-4 hours. According to the results of the study, the clinical effectiveness of Phenyramidol was determined as 65%. Of the patients participating in the study; adverse reactions were reported in 18.5% of patients receiving 100 mg Phenyramidol, 14.9% of patients receiving 200 mg Phenyramidol, and 15.7% of patients receiving 100 mg Phenyramidol + 300 mg Aspirin. The observed undesirable reactions were nausea, epigastric pain, heartburn, and itching.[23]

In 62 cases with musculoskeletal disorders evaluated in a clinical randomized study, the analgesic and muscle relaxant effects of intramuscular Phenyramidol were evaluated. 82.9% of 41 patients using intramuscular Phenyramidol had "excellent" and "good" muscle relaxant and analgesic efficacy. 81% of patients using intravenous phenyramidol had an 'excellent' and 'good' degree of antispasmodic relief. "Excellent" and "good" analgesic efficacy was observed in 90.52% of patients using intravenous phenyramidol, and "excellent" and "good" muscle relaxant efficacy was observed in 81%. Side effects observed in patients during the study were nausea, a bad taste in the mouth, and transient dizziness. It has been reported that these side effects were seen in 10 patients who were administered the drug intravenously and in 6 patients who were administered intramuscularly. It was also emphasized in the study that the incidence of side effects associated with the use of phenyramidol administered intravenously can be minimized by reducing the injection rate.[3]

In studies comparing the analgesic effect of Phenyramidol with narcotic and non-narcotic agents such as codeine and acetylsalicylic acid, it has been shown that Phenyramidol can exhibit superior analgesic efficacy compared to codeine and acetylsalicylic acid. In a separate study of 233 patients (age range 16-85 years) of both sexes, Phenyramidol demonstrated 81.5% analgesic efficacy.[11] In addition, according to the results obtained in a study where Phenyramidol was given orally from 100 mg to 400 mg, Phenyramidol was effective in relieving pain from 53.6% to 81.5%.[4] In a clinical study by Batterman et al., it was observed in studies that oral phenyramidol did not cause any toxicity even at daily dosages of up to 3200 mg.[22] In 101 pediatric patients aged 12–82 years, parenteral use of phenyramidol has been shown to provide "excellent-good" muscle relaxant and analgesic efficacy in 89% of patients.[24]

In a clinical study to evaluate the safety and efficacy of Phenyramidol in acute conditions for lumbago, integumental pain, and musculoskeletal pain, 100 patients were given 1-2 tablets of 400 mg Phenyramidol orally 2-3 times a day. The planned treatment lasted 3-7 days. When the patients were re-evaluated, it was shown that the use of oral Phenyramidol had an "excellent" and "good" safety level of 93%. As a result of the study, the researchers reported that 89% of patients using oral phenyramidol provided a clinically significant improvement. In the study, undesirable side effects were observed in 11 of 100 patients, but it was emphasized that the reported side effects were observed with 4000-8400 mg daily dosing, but none of these side effects were clinically significant.[9]

In 454 outpatients with musculoskeletal disorders, 7 types of treatment regimens involving 100, 200, 400 mg phenyramidol, 300-600 mg Acetylsalicylic acid, 600 mg acetaminophen, 50 mg ethoheptazine, 50 mg Chlormezanone, 200 mg Tranquilizer+benzlindolyethylpyridine, and placebo with dosing of 3-4 times a day were administered throughout the study. As a result of the study, patients in the 400 mg phenyramidol dosing group had the strongest analgesic effect (81.5%) compared to other analgesics evaluated in the study.[25]

In another clinical study; the efficacy and safety of parenteral 300-1000 mg/day intramuscular Phenyramidol treatment was investigated in 72 patients with low back pain, sprains, fibrositis, tenosynovitis, and tension headache who applied to both the outpatient clinic and private practice. "Excellent" and "good" recovery was observed in 68 (94.4%) of 72 patients with acute musculoskeletal conditions.[14]

In a single-blind comparative clinical study, the efficacies of Phenyramidol, Chlorzoxazone, and Hydramitrazine were compared in 48 patients (26E/22K) aged 28-72 years with a diagnosis of spasmodic torticollis. Of the 48 patients who participated in the study a separate group treatment containing 400 mg Phenyramidol, 250 mg Chlorzoxazine or 150 mg Hydramitrazine was arranged for all patients who participated in the study, 8 of whom had severe torticollis, 13 had moderate torticollis, and the remaining 27 had mild torticollis. It is reported that one tablet of Phenyramidol or Hydramitrazine or one tablet of Chlorzoxazone three times a day is administered to the patients for 2 days, and this dosing is adjusted as 3x2 when necessary. According to the results of the study, "satisfactory or complete" relief was obtained in 71% of those treated with Phenyramidol, and "satisfactory or complete" relief was achieved in 63% of those treated with Chlorzoxazone. In addition, as a result of the study, it was observed that Phenyramidol exhibited 20% more successful clinical efficacy compared to Chlorzoxazone. In the study, while the remission rates were 40% for Phenyramidol, the remission rate was 30% with Chlorzoxazone. The most common side effects seen in participants throughout the study have been observed to be fatigue and malaise.[26]

In silico, in vitro, and in vivo studies carried out in 2021, it was shown that Phenyramidol exhibited statistically significantly higher analgesic efficacy than thiocolchicoside and acetylsalicylic acid, as well as anti-inflammatory efficacy equivalent to ibuprofen and dexamethasone (Figure 1).[11]

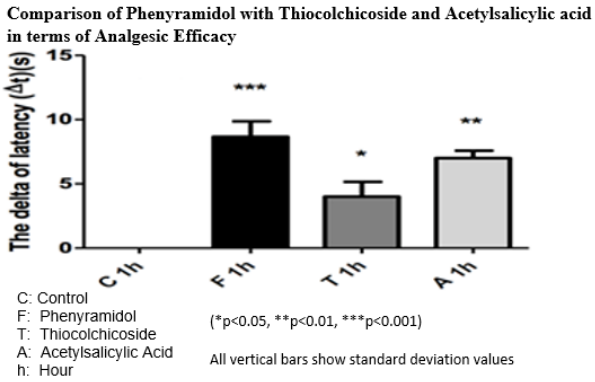

Figure 1 is adapted from reference [11].

In the study, the analgesic and anti-inflammatory activities of Phenyramidol (65 mg/kg), Ibuprofen (100 mg/kg), and Dexamethasone (1mg/kg) were tested in male albino (26.57±0.3 g; n=4-6) mice. For analgesic activity, rats were placed on a hot plate at 55°C±1°C, and the prolongation at paw licking time (Δt) was calculated and) the analgesic effects of Phenyramidol (65 mg/kg), Acetylsalicylic acid (100 mg/kg), and thiocolchicoside (0.37 mg/kg) were measured and recorded at hour 1.[11]

The anti-inflammatory effects of Phenyramidol (65 mg/kg), Ibuprofen (100 mg/kg), and Dexamethasone (1mg/kg) were measured using the carrageenan-induced paw edema test, and ibuprofen and Dexamethasone were used as positive controls. After oral administration of drugs in simple syrup, 30 minutes before the induction of edema formation with carrageenan, the levels of interleukin (IL)1β and tumor necrosis factor (TNF)-α (cytokine) were measured in the exudate liquid obtained from the paw in which Carrageen was applied, with the help of ELISA kits.[11]

Phenyramidol exhibited statistically significant higher analgesic efficacy than thiocolchicoside and acetylsalicylic acid, with the commercial fluorometric inhibitor screening test kit for anti-inflammatory activity and paw edema tests, It was observed that Phenyramidol exhibited anti-inflammatory activity equivalent to Ibuprofen and Dexamethasone, and provided balanced inhibition of the enzyme cyclooxygenase (Figure 2). It has also been reported in the study that Phenyramidol provides a statistically significant decrease in interleukin (IL) 1β and tumor necrosis factor (TNF)-α (cytokine) levels.[11]

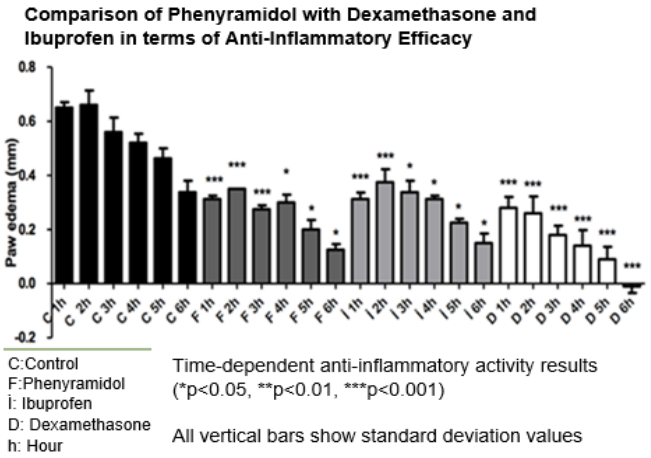

Figure 2 is adapted from reference [11].

Researchers have also proven the Phenyramidol's strong anti-inflammatory efficacy in light of the statistically significant reduction of inflammatory cytokines interleukin (IL) 1β and tumor necrosis factor (TNF)-α.[11]

Discussion

Phenyramidol has the equivalent analgesic activity to codeine.[27,28] Furthermore, adverse reactions are very unlikely in patients using Phenyramidol compared to codeine and meperidine.[6] Regardless of the etiology and duration of the pain, Phenyramidol has satisfactorily improved the painful conditions in most patients. Many studies have shown that Phenyramidol at therapeutic doses is a safe molecule in terms of the incidence of undesirable effects, primarily on the central nervous system, cardiovascular system, and gastrointestinal system.[6] Phenyramidol exhibits efficacy by producing muscle relaxation as a result of an interneuron blocking effect.[5]

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The reason for the tocolytic effect of phenyramidol is that the spinal cord exerts its efficacy on polysynaptic reflexes but not on monosynaptic reflexes.[29] Unlike other myorelaxants, phenyramidol has three different effects on the patient: analgesic effect, myorelaxant effect, and anti-inflammatory effect. Studies have shown that phenyramidol, alone or in combination with salicylates or corticosteroids, also exhibits strong clinical efficacy in the relief of pain associated with contusions, sprains, and fractures.[7] It has also been reported that phenyramidol exhibits cholesterol-lowering efficacy in rats and humans by inhibiting bishydroxycoumarin metabolism.[19]

Batterman et al. showed that the drug also exhibits analgesic and myorelaxant efficacy in ambulatory patients with neuromuscular-skeletal disorders.[20] According to the results of the study conducted in mice, Phenyramidol, Codeine, and Meperidine are of equal potency to each other in terms of analgesic efficacy.[4] Compared to Codeine, Phenyramidol has an analgesic effect without causing CNS depression.[4] While it has been reported that phenyramidol is effective and well-tolerated in acute lumbago, musculoskeletal pain, and integumental pain when used for up to 7 days, it is emphasized in studies that caution should be exercised when using this group of drugs for long-term use in patients with liver disease and in combination with drugs known to cause liver damage.[9]

In a clinical study, the efficacy of phenyramidol was shown to be related to dosing. However, it has been reported that it can cause CNS depression at very high doses.[30] In a study conducted with Phenyramidol in silico, in vitro, and in vivo environments in 2021, anti-inflammatory and analgesic effects were investigated based on the pharmacophore group similarity of Phenyramidol and oxicams. As a result of the study, it was observed that Phenyramidol provided statistically significant higher analgesic efficacy than thiocolchicoside and acetylsalicylic acid, as well as anti-inflammatory efficacy equivalent to Ibuprofen and Dexamethasone, together with balanced cyclooxygenase enzyme inhibition. It has also been reported in the study that Phenyramidol provides a statistically significant decrease in the levels of inflammatory mediators such as interleukin (IL) 1β and tumor necrosis factor (TNF)-α (cytokine).[11]

It is known that inflammation and inflammatory mediators such as interleukin (IL) 1β and tumor necrosis factor (TNF)-α are present in all painful musculoskeletal diseases. Phenyramidol's existing analgesic and myorelaxant effects, as well as its anti-inflammatory activity and its role in the regulation of inflammation, will differentiate it from other centrally acting myorelaxants, especially in the treatment of chronic and painful musculoskeletal diseases. Phenyramidol is the first choice in the symptomatic treatment of painful musculoskeletal system diseases with its anti-inflammatory effectiveness, as well as being an agent that can be preferred in painful chronic musculoskeletal patients, who need narcotic agents with its fast analgesic efficacy that starts at 15 minutes, equivalent to Codeine, even in long-term use. It is a preferred treatment option.

Conclusion

Phenyramidol, which contains three pharmacological efficacies that are statistically significant potent analgesic, myorelaxant and anti-inflammatory in studies, is an effective and safe treatment option that provides up to 94% improvement in painful musculoskeletal disorders and is tolerable in 96.8% of patients. Phenyramidol, with its analgesic, myorelaxant and anti-inflammatory effects, is a treatment option that can be used as the first choice in the symptomatic treatment of painful musculoskeletal diseases.

Acknowledgments

None.

Conflicts of interest

Fatmanur Otmar Ozcan, Kubra Saygisever-Faikoglu and Gokhan Faikoglu,are medical advisors of Recordati.

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